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ANTIBIOTICS TODAY*

SELMAN A. WAKSMAN

Professor Emeritus, Institute of Microbiology
Rutgers—The State University, New Brunswick, N. J.

INTRODUCTORY REMARKS

I AM very grateful for the honor that you are conferring upon me on this occasion. The name of Rudolph Virchow brings forth in my mind some very exciting memories. A general impression still prevails in scientific circles that Virchow, the father of "cellular pathology," was a strong opponent of bacteriology. Such eminent bacteriologists as Klebs and Behring have attacked Virchow for his lack of appreciation of the progress made in such important fields as the causation and nature of diseases, e.g., of cholera, diphtheria, and tuberculosis. Virchow was not prepared to adjust himself immediately to the epoch-making discoveries of Pasteur. It was said that Virchow "grew up in the shadow of anticontagionism," which he outgrew later, however, as was demonstrated by his enthusiasm over Koch's work. His own later investigations in the fields of mycosis and parasitology, notably trichinosis, showed clearly his changing attitude. Virchow was particularly interested in the toxic substances produced by bacteria, as well as in the

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effects of purely chemical toxins or poisons on body cells. Nevertheless, he emphasized the fact that cellular pathology contributes to our understanding of the relation between drugs and the cells of the body. He now praised Pasteur's work as having "opened new avenues to medicine and technology," still insisting, however, upon the "social and constitutional factors"' in the causation of disease (Ackerknecht). In his *History of Pathology*, E. R. Long states: "We are all cellular pathologists today, taking our post-Virchowian cellular sense for granted."

The introduction of antibiotic and other chemotherapeutic agents in the treatment of infectious diseases may be said to help bridge the possible confusion in our understanding of the functions of the cell and of the invading microbe.

Historical

Seldom in the history of medical science has such rapid progress been made in the fundamental and practical aspects of the healing arts as during the past 25 years. This has been due in no small measure to the advances made in the knowledge and application of antibiotics.

It was known before 1940 that various groups of microbes are capable of producing chemical substances that have the capacity to exert an inhibiting effect upon the growth of other microbes and, actually, even to destroy them. During the period from 1938 to 1940, these potentialities became fully established. It was recognized that various saprophytic organisms are capable of inhibiting the growth of different disease-producing bacteria, fungi, and protozoa. The further discovery that such organisms are capable of forming new types of chemical compounds that possess desirable mechanisms for destroying disease-producing microbial agents has laid the basis for a new approach to chemotherapy. New drugs were placed at the disposal of the physician and the veterinarian for combating infectious diseases of man and animal. The nutritionist gained knowledge of a new type of compound that would increase the growth of domesticated animals. New agents became available for the preservation of our food supplies and other essential biological preparations, such as vaccines and viruses.

The formation of an antibiotic designated by Fleming in 1928 as penicillin was found in a culture of a fungus. In 1940 it was demonstrated that this compound could be used in the treatment of various

infectious diseases caused by Gram-positive bacteria, cocci, and spirochetes. These diseases are now being treated quite successfully on a scale never dreamed of before. Another antibiotic, actinomycin, was isolated in 1940 from a culture of an actinomycete. It was highly effective against a number of bacteria. Unfortunately, it was too toxic for therapeutic use. Soon afterward (1943) another antibiotic, designated as streptomycin, was isolated from a culture belonging to the actinomycetes. It proved to be effective against infections caused by Gram-negative bacteria as well as Gram-positive organisms resistant to penicillin. It was also effective in the treatment of tuberculosis. Various other antibiotics were found to be produced by bacteria, notably the aerobic spore formers. It is sufficient to mention tyrothricin, isolated in 1939, later followed by bacitracin, polymyxin, and others. Some of these are also used effectively in the treatment of certain diseases caused by Gram-positive and Gram-negative bacteria. Thus the year 1940 may be said to have laid the foundation for the use of antibiotics in the treatment of infectious diseases.

A feverish search was now begun in numerous laboratories throughout the world, especially in the United States and in Great Britain, for other antibiotics that could be effective against diseases not previously amenable to therapy or that had become resistant to the known chemotherapeutic agents. In rapid succession came chloramphenicol, the tetracyclines, the neomycins, and erythromycins, followed later by numerous others.

Various diseases, beginning with those caused by the so-called "larger viruses," or the lymphogranuloma-psittacosis group of intracellular parasites, trichomonal, amoebic, and other protozoan infections, and numerous others caused by bacteria and fungi could now be treated successfully by means of drugs produced by microbes, namely the antibiotics.

The microbiologist was now successful in obtaining more efficient strains of antibiotic-producing organisms, of improving culture media, thus increasing the yields of the antibiotics, and of developing new techniques for their isolation. The chemist succeeded in making new derivatives of natural antibiotics, such as dihydrostreptomycin, the tetracyclines, and certain others that were less toxic or more effective. Numerous synthetic compounds soon made their appearance, thereby supplementing the antibiotics in the treatment of infectious diseases.

The pharmacologist succeeded in improving the efficiency of the drugs and reducing their toxicity. The clinician has made use of this accumulated knowledge to eliminate the danger from infectious diseases and help increase the life span of man.

Production of Antibiotics

From being a mere curiosity a quarter of a century ago, the antibiotics have come to occupy an important place in human, in animal and, to some extent, in plant therapy. Several thousand chemical compounds or preparations have now been isolated from numerous cultures of microorganisms. Of these, about 80 have found practical application in disease control. Among the antibiotic-producing organisms the actinomycetes have come to occupy an important place as producers of antibiotically active substances. More than 500 preparations have been obtained from this group of organisms, especially from members of the genus *Streptomyces*. Of these, about 50 have found practical applications (Waksman and Lechevalier).

Most antibiotics are not formed by the various microorganisms as single chemical entities, but as groups of closely related chemical compounds. Different species may produce slightly different modifications of the same type of compound. Thus the neomycin complex is made up not only of two closely related forms (neomycins B and C), but also of the neamine, catenulin (paromomycin), kanamycin, and a variety of others. Neomycin itself can be formed by different species of *Streptomyces*. Various actinomycetes are capable of forming several other basic antibiotics in a number of different modifications, as in the case of the streptothricins. Each antibiotic preparation may consist of several chemical modifications of the same compound, which are also characterized by different biological properties.

The same thing is true of the tetracyclines, the erythromycins, the polyenes, and various other antibiotics. Variations in structure and in activity have presented numerous puzzling problems to the microbiologist, the chemist, the pharmacologist, and the clinician. In the case of the tetracyclines, we find not only the chlor- and oxy-compounds, but also tetracycline itself, as well as demethyl-tetracycline and a host of other derivatives. The macrolides represent a large number of substances, varying in chemical structure and biological activity. This is even more true of the polyenes, especially the tetraenes, the

hexaenes, and the heptaenes, all of which are characterized by strong antifungal and limited antibacterial properties; they vary greatly in toxicity and in nature of the antifungal spectra.

Recognition of the potential antitumor properties of the actinomycins has greatly stimulated studies of this group of antibiotics. Almost all the capital letters of the alphabet have been used to designate the different forms that have been isolated all over the world from different cultures of *Streptomyces*. Roman numerals and Greek letters have been added to supplement this system of designating the more than 50 actinomycin preparations now known. By feeding the actinomycin-producing cultures different amino acids and by developing new methods for the isolation and separation of the individual chemical entities, much has been learned in the elucidation of this group of compounds. All the actinomycins now known are characterized by a high toxicity, considerable activity against Gram-positive bacteria, and some degree of potency against certain neoplasms.

The chemical differences among the various antibiotics are always accompanied by corresponding differences in their biological properties, especially toxicity and antimicrobial activity or antibiotic spectrum. These properties are of great importance in determining the practical utilization of the particular antibiotic preparations in the treatment of specific diseases.

The screening programs for new antibiotics are still proceeding at an unending pace. Particular attention is now being paid to substances that might prove effective against tumors and the true viruses. The new preparations are being constantly isolated and tested for their effectiveness in experimental animals, in tissue cultures, in egg embryos, and by a variety of other procedures. A number of antitumor preparations have been isolated, including, in addition to actinomycin, also azaserine, sarcomycin, carzinophilin, mitomycin, olivomycin, and pectamycin. They are all highly toxic and possess only limited practical application.

Certain antibiotics can be modified chemically to yield products with more desirable or at least somewhat different properties. Of particular interest is the recent introduction of the so-called "semisynthetic" penicillins, or those penicillins that have been modified in chemical structure and in biological effectiveness by the use of enzyme systems and by chemical synthesis. Streptomycin can be reduced to dihydrostreptomycin, and chlortetracycline to tetracycline; chemical

modifications of the inactive part of the chloramphenicol molecule to render it active are other illustrations.

The Problem of Resistance

Among the more important problems in the field of antibiotics now receiving considerable attention are those concerned with the phenomena of resistance. The practice of combining two or more antibiotics, or an antibiotic with a synthetic compound has undergone much criticism. Such combinations have worked well in the treatment of tuberculosis, as by combining of streptomycin with PAS or with isoniazid. The nature and concentration of these combinations are usually modified in the treatment of particular cases, depending on the nature and state of the disease. Cases of tuberculosis that have become resistant to these three drugs are now treated with viomycin or cycloserine, alone or together with ethionamide or other synthetic or antibiotic compounds.

Considerable success has also been experienced in the use of two antibiotics, such as penicillin and streptomycin, or of an antibiotic, such as neomycin, with a steroid. The possible danger of development of resistance to both antibiotics at the same time suggested the elimination of such a practice. The development of resistance to penicillin among the staphylococci has become a very serious problem. Several new antibiotics, beginning with erythromycin, novobiocin, and vancomycin, followed by others, tend to replace older drugs whenever resistance has developed. The synthetic or rather semisynthetic approach to the modification of the antibiotic molecule has been particularly successful in the case of penicillin, rendering it more resistant to the action of penicillinase or more active upon bacteria that have tended to develop resistance to the natural penicillins.

Antitumor Substances

Numerous preparations have now been isolated that possess remarkable activity against certain neoplasms. Unfortunately, only a few of them have found a certain place in the treatment of this group of diseases. Actinomycin was the first antibiotic to have shown such limited potentialities. This antibiotic and some others isolated more recently are too toxic or are not sufficiently active. They are not very prom-

ising, as compared to the treatment of infectious diseases by antibiotics. These compounds vary greatly in their chemical nature and in their biological activity. Some are active against neoplasms and bacteria, others against neoplasms and fungi, and still others against neoplasms alone. The neoplasms vary greatly in their sensitivity to different agents; just as, in the case of bacterial or fungal sensitivity to various antibiotics, an antitumor spectrum can be observed.

Antiviral Substances

Even less progress has been made thus far in the search for antiviral agents. In spite of the fact that we now possess numerous compounds that are active against virtually all saprophytic and pathogenic bacteria, fungi, and protozoa, none of them is known to be active upon the small or true viruses. The excitement created by the isolation of the "broad spectrum" antibiotics, with the possibility of their action upon viruses, soon abated when it was discovered that their activity embraced only the so-called "large viruses," or the intracellular parasites of the lymphogranuloma-psittacosis group. The small viruses are not living systems, in a proper sense; they do not grow, do not metabolize, and do not multiply. They are inductors of reactions, thus endowing the host cells with a change in their metabolic processes from "normal" to "abnormal," thereby causing them to form more viruses of the same kind rather than carry out normal metabolic and growth reactions. A logical approach to the control of the viruses must be quite different from that utilized in the isolation of antibiotics.

Among the recently isolated antiviral agents, mention may be made of the following: mutomycin, myxoviromycin, nitromycins, quinomycin (this was said to have a prophylactic effect for poliomyelitis in mice), rutilantin (shown to possess antiphage activity), and violarin B.

Antibiotics in Clinical Medicine

Antibiotics continue to occupy an important, if not a leading, place in the practice of medicine. This is true particularly of the treatment of infectious diseases caused by bacteria and other microorganisms. Only a few recent contributions may be cited:

The sensitivities of 621 strains of Gram-negative bacteria isolated from patients with clinical infections brought out the fact (Petersdorf

et al.) that chloramphenicol was the most effective agent against *Escherichia coli;* neomycin and kanamycin against *Klebsiella;* polymyxin B against *Pseudomonas;* and penicillin against *Proteus mirabilis.* The extensive use of antibiotics against gonococci led to progressive decrease of sensitivity of the organisms to penicillin and streptomycin. Out of 327 strains studied (Roiron *et al.*), 72.4 per cent were sensitive to 50 μg./ml. of streptomycin, recovery being obtained in 73.14 per cent of the cases; 22.9 per cent of the strains were resistant to a concentration of 1,000 μg./ml. streptomycin, and recovery was observed in 6.1 per cent of the cases only. Strains resistant to streptomycin were less sensitive to penicillin than nonresistant strains. All strains were sensitive to tetracycline and to spiramycin.

Today's Problems

Numerous problems in the field of antibiotics still remain either unsolved or insufficiently understood. They are of both theoretical and practical significance. Some of them may be listed here:

The actual role of the antibiotics in the life of the organisms producing them is unclear.

Since antibiotics are formed largely by soil-inhabiting microorganisms, the question whether they play any role in the ecological relationships of these organisms often arises.

The mechanism of development of resistance by some bacteria and not by others still leaves much to be elucidated. The same is true of the rates of development of resistance against different antibiotics.

The formation of bacterial strains that become nutritionally dependent upon certain antibiotics, as in the case of streptomycin, has aroused much speculation but still remains largely unexplained.

The mode of action of antibiotics upon different bacteria is now receiving considerable attention.

Whatever the final answer to these and other questions will be, we may well conclude that the antibiotics have made and will no doubt continue to make important contributions of great theoretical and practical significance to our understanding of certain natural processes, to provide tools for the solution of fundamental biological problems and, most important, to the alleviation and control of the numerous infectious diseases of man, animals, and plants. The future is rich in potentialities. It is bound not only to supplement but to increase greatly our

store of knowledge of a highly important group of chemical substances produced by microbes, to broaden the armamentarium of the medical profession, and to contribute towards an increase of our food supply.

SUMMARY

It is just a quarter of a century since the antibiotics became recognized as an important group of chemical compounds produced by microorganisms, and their practical applications in the control of numerous infectious diseases established. The isolation of gramicidin from a culture of a soil bacillus, the reinvestigation of the production of penicillin by a culture of fungus, and the isolation of actinomycin from an actinomycete, marked the beginning of a new era in medical science and in veterinary practice that came to be designated as the era of antibiotics. In this brief period of time the treatment of infectious diseases of man, animals, and plants caused by bacteria, fungi, and other microscopic forms of life has been revolutionized. Antibiotics have also contributed in many other ways toward the improvement of man's health, the supply of available food, the preservation of various foodstuffs and various other biological products.

However, as in the case of other great discoveries, the extensive use of antibiotics, resulting in the elimination of many infectious diseases and in a marked increase in the life span of man, has brought with it new problems, some clinical and others social in nature. The development of resistance among sensitive organisms to known antibiotics has led to the search for new substances produced either biologically or synthetically, and to the use of combinations of antibiotics and synthetic compounds. Important diseases, notably those caused by viruses as well as those of unknown etiology, still remain largely resistant to chemotherapy. Numerous efforts are being directed toward the discovery of compounds that would do for these diseases what antibiotics have done for diseases caused by bacteria and other microorganisms.

New antibiotics are being constantly isolated. Some of these have proved to be highly promising in increasing the armamentarium of the medical profession for combating diseases that have afflicted mankind since time immemorial.

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